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Major Postoperative Complications Are a Risk Factor for Impaired Survival after CRS/HIPEC

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ABSTRACT

Background. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a combined treatment option for well-selected patients with peritoneal carcinomatosis (PC). The study aimed to identify factors influencing cancer-specific survival (CSS) and disease-free survival (DFS).

Methods. Data of 113 patients with colorectal or appendicular carcinomatosis from a single center operated between 2009 and 2014 were retrospectively collected and analyzed. Patients with high-grade tumors received standard perioperative chemotherapy, and patients with low-grade appendix tumors were directly operated. HIPEC was performed after radical CRS.

Results. Patients had carcinomatosis from appendix neoplasms in 63% (71/113), including low-grade and high-grade tumors, and colorectal cancer in 37% (42/113). Complete cytoreduction and HIPEC were possible in 67% of patients. Major morbidity occurred in 10.6% of patients, and mean follow-up was 28 months. For colorectal PC, median CSS and DFS were 40 and 12 months, respectively. Median DFS was 19 months for high-grade appendix tumors, while median CSS has not been reached. All patients with diffuse peritoneal adenomucinosis were still alive at time of analysis; rate of DFS was 96% for these patients after 3 years. Major postoperative complications (Clavien-Dindo IIIB or higher) and positive nodal state were associated with impaired CSS and DFS, while a peritoneal cancer index score of >10 was independently associated with impaired CSS.

Conclusions. CRS/HIPEC offers a survival benefit in well-selected patients with PC. Major postoperative complications affect long-term oncologic outcome of these patients.

The combination of radical cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) can improve cancer-specific survival (CSS) in well-selected patients with peritoneal carcinomatosis (PC) of colorectal (CRC) or appendix tumors.[1] The outcome depends on multiple factors, such as the subtype of the primary tumor, the extent of carcinomatosis as defined by the peritoneal cancer index (PCI), and the radicality of surgery (completeness of cytoreduction [CC] score).[2] Modern systemic therapy has made tremendous advances, and recent regimens—for example, the combination of FOLFOXIRI and bevacizumab—provide a median progression-free and overall survival (OS) of 12 and 31 months, respectively.[3] However, a previous subgroup analysis of 2 randomized trials suggests an impaired survival for patients with PC compared to other hematogenous metastatic sites.[4]

Despite the availability of a randomized trial, the benefit of CRS/HIPEC over modern systemic chemotherapy alone has not yet been proven.[5,6] This is mostly due to methodologic shortcomings, such as the availability of novel agents for the control group, and different operative strategies or selection criteria. For CRC and appendicular tumors, however, there is evidence from multicenter databases and case series showing better OS for colorectal patients and long-term disease-free survival (DFS) for low-malignant appendix tumors.[2,7] Furthermore, it has been shown that this maximally invasive procedure can be performed with acceptable mortality and morbidity rates.[8] As a consequence, CRS/HIPEC became a treatment option for many patients with peritoneal surface malignancies.

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The critical question today is the selection of patients for CRS/HIPEC to avoid unnecessary procedures in patients who will not benefit from surgical treatment. Preoperatively known clinical disease criteria may help select patients. This is probably the true benefit of analyses of patient registry outcomes while still awaiting results from randomized trials.

We retrospectively analyzed CSS and DFS of a patient cohort with PC from appendiceal or CRC origin and performed univariate and multivariate analysis to identify factors predicting outcome in regard to CSS and DFS. Furthermore, we analyzed the recurrence patterns to gain a better understanding about disease relapse after CRS/HIPEC.

METHODS

A complete cohort of patients with PC of CRC of appendiceal origin scheduled for CRS/HIPEC in our department between January 2009 and December 2014 was analyzed. The primary outcome was CSS from the date of the operation. Secondary outcomes were DFS, determination of patterns of recurrence, and identification of factors predicting CSS and DFS. The study was approved by the responsible ethics committee (KEK-ZH-Nr. 2016-00118) of the cantonal authorities in Zurich, Switzerland.

Patients were selected for CRS/HIPEC after clinical assessment and exclusion of extra-abdominal tumor manifestations by positron emission tomography/computed tomography. All patients were presented in a multidisciplinary tumor board before treatment. Patients with CRC or high-grade (HG) appendiceal tumors received standard-of-care perioperative chemotherapy based on leucovorin, 5-fluorouracil, irinotecan and/or oxaliplatin in combination with monoclonal antibodies targeting angiogenesis where appropriate. Patients with low-grade (LG) appendix tumors were directly operated. The group of LG appendiceal neoplasms corresponds to the entity of diffuse peritoneal adenomucinosis (DPAM) according to the classification of Ronnett et al.[9] The HG appendix tumor group includes mucinous tumors with high cellularity (peritoneal mucinous carcinoma, PMCA) and adenocarcinomas of intestinal or signet-ring type. Anesthesia was conducted with propofol and volatile anesthetics combined with thoracic epidural anaesthesia as described previously.[10] HIPEC was performed with an open abdomen/colosseum technique as specified elsewhere, using 1.5% glucose peritoneal dialysis solution for perfusion.[11,12] Mitomycin C (30 mg/m^2) and doxorubicin (15 mg/m^2) were used in combination in all cases. A complete procedure was defined as radical CRS (CC score of 0 for HG appendix tumors/CRC and CC score of 0 or 1 in case of LG appendiceal neoplasms/DPAM) followed by HIPEC in full concentration at 42 °C over 90 min. Follow-up included clinical examinations, tumor markers, and computed tomographic scans every 6 months. Adjuvant chemotherapy was provided according to recommendations of an interdisciplinary tumor board.

Statistics

Continuous data are provided as median ± interquartile range (IQR). The Mann–Whitney *U* test or Pearson's Chi square test was used to compare medians and their respective odds in the baseline groups. Kaplan–Meier curves and survival tables were calculated to determine CSS and DFS in subgroups from the date of the operation until date of cancer-related death, disease progression, or date of last follow-up in months. The Mantel-Cox log rank test was used to test for differences between survival curves. Univariate and multivariate analyses were performed by Cox regression. Results of the univariate analysis were bias corrected by bootstrapping 1000 samples. Multivariate analysis was performed with a backward conditional likelihood ratio model with initial inclusion of all variables and consequent stepwise exclusion. Missing values were replaced with the mean of the respective variable for multivariate analyses. All statistical analyses were performed by IBM SPSS 23 for Windows. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient Characteristics

Overall, 113 patients with PC of either appendiceal origin ($n = 71$, 31 LG and 40 HG tumors) or CRC ($n = 42$) were operated between January 2009 and December 2014. Patients had a median age of 52 years (IQR 43–59) and with an equal gender incidence (56 male and 57 female patients). Mean follow-up at time of analysis was 28 months. A complete procedure was possible in 76 patients (67.3%). Reasons for incomplete interventions were preoperative underestimation of PC by imaging modalities and inability to perform a complete resection. More precisely, in 12 patients the abdomen was closed after laparotomy or laparoscopy and initial inspection, 10 patients received surgical cytoreduction without HIPEC, and 15 patients had CRS/HIPEC but without achieving a CC score of 0. Overall morbidity rate was 41.7%. Major complications, defined according to Clavien-Dindo IIIB or higher (need for reoperation or intensive care unit referral), occurred in 12 patients (10.6%).[13] No 90-day mortality was observed. Table 1 summarizes the details of the patient characteristics and surgical procedures.

TABLE 1 Tumor and operative characteristics of 113 patients undergoing CRS/HIPEC for PC of colorectal or appendiceal origin

Parameter	Appendix tumors ($n = 71$, 62.8%)	Colorectal carcinoma ($n = 42$, 37.2%)	P value
Histologic type			<0.001
DPAM	31 (43.7%)		
PMCA	14 (19.7%)		
Intestinal type AC	15 (21.1%)	37 (88.1%)	
Signetring type AC	10 (14.1%)	5 (11.9%)	
Adenocarcinoid	1 (1.4%)		
Appearance of PC			0.015
Synchronous	47 (66.2%)	18 (42.9%)	
Metachronous	24 (33.8%)	24 (57.1%)	
Praeoperative Chemotherapy	17/71 (23.9%)	37/42 (88.1%)	<0.001
Agents			
FOLFOX/FOLFIRI only	9	17	
+ targeted therapy	8	20	
Cycles	12 (6.5-12)	8.5 (6-12)	
Postoperative Chemotherapy	24/71 (33.8%)	28/42 (66.7%)	0.001
Agents			
FOLFOX/FOLFIRI only	11	7	
+Targeted therapy	13	21	
Cycles	12 (6–12.5)	10 (6–12)	
Nodal status			<0.001
pN0	20 (28.2%)	10 (23.8%)	
pN1	5 (7.0%)	6 (14.3%)	
pN2	7 (9.9%)	24 (57.1%)	
pN3	0	1 (2.4%)	
Nx	39 (54.9%)	1 (2.4%)	
Grading			
G1	36 (50.7%)	0	<0.001
G2	4 (5.6%)	22 (52.4%)	
G3	16 (22.5%)	15 (35.7%)	
Unknown	15 (21.1%)	5 (11.9%)	
Surgery			
Operation time (min)	580 (370–780)	504 (420–634)	0.184
Blood loss (ml)	250 (100–637.50)	200 (100–500)	0.984
Median PCI overall	15(5–27)		
Median PCI subgroups	21 (8–34)	6.5 (3.75–11)	<0.001
Complete CRS/HIPEC performed	47/71 (66.2%)	29/42 (69%)	0.7
PCI of completely treated patients	15 (4–25)	6 (3.5–8.5)	0.004
ICU stay (d)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.755
Hospital stay (d)	16.0 (12–24)	15.50 (12–20)	0.524

Interval data are shown as median with 1–3 interquartile range. Categorical data are shown as absolute values (n =) and percent of the respective total patient number

Mann-Whitney U-Test was used to test for differences between groups with interval data. Comparison in categorical data was performed using Pearson-Chi Square test

HIPEC hyperthermic intraperitoneal chemotherapy, *PC* peritoneal carcinomatosis, *DPAM* diffuse peritoneal adenomucinosis, *PMCA* peritoneal mucinous carcinomatosis, *AC* adenocarcinoma, *PCI* peritoneal cancer index, *ICU* intensive care unit

CSS after Complete CRS/HIPEC

After radical CRS/HIPEC, the median CSS for patients with CRC ($n = 29$) was 40 months, while the median CSS for HG appendix tumors ($n = 19$) has not been reached. All patients ($n = 28$) with LG appendix tumors were still alive at the time of analysis ($n = 28$) (Fig. 1a). Three-year CSS rates were 74% for HG appendix tumors and 66% for CRC. Survival of LG appendix tumors was significantly better than for HG ($p = 0.004$) or CRC ($p = 0.001$) patients. Remarkably, there was no difference between HG appendix and CRC patients ($p = 0.614$). In contrast, survival was significantly impaired in incompletely resected patients, with a median CSS of only 13 months for patients with CRC ($n = 13$; $p \leq 0.001$) and 24 months for HG appendix tumors ($n = 21$; $p = 0.011$). None of the three patients with incompletely resected DPAM had died of disease at last follow-up.

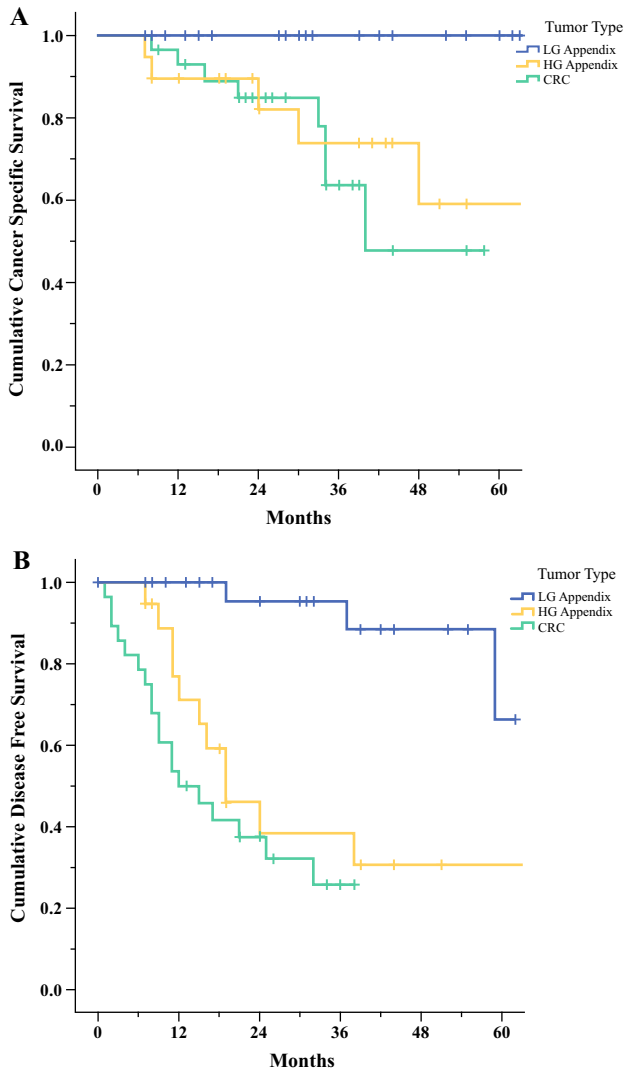

FIG. 1 CSS (**a**) and DFS (**b**) after complete CRS/HIPEC ($n = 76$). **a** All patients with LG appendix tumors were still alive after 60 months. Median OS for HG appendix tumors has not been reached, while it was 40 months for patients with CRC. Survival of LG appendix tumors is significantly better than for HG ($p = 0.004$) or CRC ($p = 0.001$) patients, respectively. In contrast, there is no difference between HG appendix and CRC patients ($p = 0.614$). **b** Median DFS (mDFS) was 12 months for CRC and 19 months for HG appendix tumors. For LG appendix tumors, mDFS has not yet been reached. DFS of LG appendix tumors is significantly better than for HG ($p \leq 0.001$) and CRC patients ($p \leq 0.001$). In contrast, there is no difference between HG appendix and CRC patients ($p = 0.254$). Vertical bars imply censoring event. Analysis was performed via construction of Kaplan-Meier curves. Mantel-Cox log rank test was used to test for differences between groups

DFS after Complete CRS/HIPEC

DFS after 3 years was 26% in patients with CRC, and 38 and 96% for HG and LG appendix tumors, respectively. Median time until recurrence of disease was 12 months for CRC and 19 months for HG appendix neoplasms, while the corresponding value has not been reached for LG appendix tumors after 60 months (Fig. 1b). DFS of LG appendix tumors was significantly better than for HG or CRC tumors ($p \leq 0.001$ for both). In contrast, there was no difference between HG appendix and CRC patients ($p = 0.254$).

Patterns of Recurrence after Complete CRS/HIPEC

A total of 34.5% of patients with PC from CRC remained free of disease, while 65.5% developed recurrence during the observation period. Only 13.8% of patients showed isolated locoregional recurrence. The majority presented with a combination of locoregional and distant recurrence (24.1%) or distant relapse only (27.4%). However, recurrence included the peritoneal cavity in up to 38% of the patients, reflecting the role a local disease control. Patients with appendix tumors showed a recurrence rate of 31.9%. Most recurrences were isolated in the peritoneal cavity; only three patients developed distant metastases. CSS was most impaired in patients with multifocal recurrence compared to patients without disease relapse ($p = 0.008$), reflecting the aggressive tumor biology in this subgroup, while patients with distant recurrence only ($p = 0.056$) had a slightly better survival. An isolated peritoneal relapse pattern was associated with the best course of the 3 recurrence patterns ($p = 0.288$).

Univariate and Multivariate Analysis of Predictive Factors

Subsequent univariate and multivariate analysis was performed on completely resected HG tumors ($n = 48$; 29 CRC and 19 HG appendix tumors) only, as no patient with DPAM died and only 3 experienced disease recurrence

during the observation period. A PCI of ≥10 and major postoperative complications significantly influenced CSS in univariate analysis (Table 2). The subsequently calculated multivariate model confirmed PCI of ≥10 and major complications to be predictors of long-term survival and furthermore included positive nodal status. Univariate analysis for DFS revealed major complications and positive N stage as significant parameters. Multivariate analysis confirmed N stage and major complications as the most important variables and showed a trend for synchronous appearance of PC (Table 3).

DISCUSSION

The present study observed and confirmed a survival benefit in selected patients with PC from CRC and appendix tumors after CRS/HIPEC. Among patients after complete CRS/HIPEC, we identified a PCI of ≥10 as negative prognostic factor for CSS, while nodal involvement is a risk factor for shortened CSS and DFS. To our surprise, major postoperative complications emerged as a significant variable influencing both recurrence and survival.

TABLE 2 Univariate and multivariate analysis of factors predicting cancer-specific survival in patients with high-grade tumors after complete CRS/HIPEC ($n = 48$)

Variable	*N*	Median CSS (Months)	Univariate analysis		Multivariate analysis	
			p-Value	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)
Age						
<50	20	40 m	0.329	0.573 (0.188–1.751)	–	–
50	28	Not reached	0.621		–	
Gender						
Male	23	Not reached	0.621	0.751(0.250–2.259)	–	–
Female	25	Not reached	–			
Tumor type						
HG appendix tumor	19	Not reached	0.618	–	–	–
CRC	29	40 m	–	–		–
T-stage						
T3	15	Not reached	0.660	–	–	–
T4	27		–	–	–	–
N-stage						
NO	13	48 m	0.126	–	0.015	8.336 (1.514–45.88)
N+	29	40 m	–	–	–	–
Signet-ring cell histology						
No	44	Not reached	0.015	–	–	–
Yes	4	12 m	–	–	–	–
Temporal appearance of PC						
Synchronous	22	Not reached	0.546	–	–	–
Metachronous	26	Not reached	–	–	–	–
Peritoneal cancer index						
<10	37	Not reached	0.026	–	0.011	4.810 (1.436–16.11)
10	11	30 m	–	–	–	–
Major complication or reoperation (Clavien-Dindo-score III B)						
No	44	Not reached	0.014	–	0.017	4.618 (1.317–16.20)
Yes	4	20 m	–	–	–	–

Hazard Ratios and respective *p*-values were calculated with cox regression analysis. To assess for bias and confounders, multivariate analysis was performed with a backward conditional model with initial inclusion of all variables and consequent stepwise exclusion of variables until the best model to fit the data was reached

HIPEC hyperthermic intraperitoneal chemotherapy, *CRS* cytoreductive surgery

Statistically significant results are bold and marked with asterisk

TABLE 3 Univariate and multivariate analysis of factors predicting disease-free survival in patients with high-grade tumors after complete CRS/HIPEC ($n = 48$)

Variable	*N*	Median CSS (Months)	Univariate analysis		Multivariate analysis	
			p-Value	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)
Age						
<50	20	12 m	0.307	0.686 (0.333–1.413)	–	–
≥50	28	21 m			–	–
Gender						
Male	23	19 m	0.733	0.882 (0.430–1.810)	–	–
Female	25	16 m			–	–
Tumor type						
HG appendix tumor	19	19 m	0.266	1.238 (0.850–1.804)	–	–
CRC	29	12 m			–	–
T-stage						
T3	15	11 m	0.599	0.800 (0.349–1.838)	–	–
T4	27	21 m				
N-Stage						
NO	13	Not reached	0.023	4.805 (1.216–13.73)	0.016	2.804 (1.210-6.496)
N+	29	15 m				
Signet-ring cell histology						
No	44	19 m	0.120	2.329 (0.803–6.753)	–	–
Yes	4	8 m				
Temporal appearance of PC						
Synchronous	22	19 m	0.306	1.477 (0.700–3.116)	0.079	2.062 (0.920–4.621)
Metachronous	26	12 m				
Peritoneal cancer index						
<10	37	19 m	0.127	1.858 (0.839–4.117)		
≥10	11	16 m				
Major complication or reoperation (Clavien-Dindo-score IIIB)						
No	44	19 m	0.007	4.731 (1.520–14.72)	0.014	4.207 (1.333–13.27)
Yes	4	7 m				

Hazard Ratios and respective p-Values were calculated with Cox Regression Analysis. To assess for bias and confounders, multivariate analysis was performed with a backward conditional model with initial inclusion of all variables and consequent stepwise exclusion of variables until the best model to fit the data was reached

HIPEC hyperthermic intraperitoneal chemotherapy, *CRS* cytoreductive surgery

Statistically significant results are bold and marked with asterisk

Patients with PC of colorectal origin can reach a median CSS of 40 months. Those results compare to data published by other specialized groups reporting a median CSS of 33 months, which is clearly superior to the median OS of 12 months only in patients with PC treated with conventional chemotherapy.[2,4,14] Our survival data also reinforce the results of the first randomized controlled trial comparing CRS/HIPEC versus chemotherapy alone in patients with PC from CRC, which showed a survival benefit of a year.[5,6] The median DFS of 12 months in our patients is also comparable to reported results.[2,14]

The outcome for patients with HG appendix tumors is comparable to CRC, with only 37% alive and 32% free of disease after 5 years. These results are inferior compared to published data, which report a 5-year OS of 59%.[7] However, this cohort included PMCA only, while our analysis incorporated patients with PMCA as well as intestinal and signet-ring type adenocarcinomas. While no definite data regarding the specific outcome after CRS/HIPEC of those HG subgroups are available, it has been shown in prior studies that outcomes for intestinal and signet-ring adenocarcinomas are worse than for PMCA.[15–17]

In contrast, in patients with LG appendicular neoplasms, we observed excellent long-term CSS and DFS. Although DPAM is normally not a rapidly progressing disease, patient morbidity still was high before the upcoming CRS/HIPEC. Treatment consisted of repeated surgical debulking. In one of the most recent reports, median DFS after CRS only was 24 months.[18] OS within our patients with DPAM was excellent in our analysis, as has been reported from several other centers.[7,19] Median DFS has not yet been reached but confirms the data of other groups, which show periods between 35 and 98 months.[7,19] As a result of the convincing data, CRS/HIPEC can today be considered the standard of care for DPAM.

Our analyses furthermore confirmed the results of previous articles identifying positive nodal status as being an important predictor of shortened DFS and CSS.[20,21] The observed patterns of recurrence agree with previous reports demonstrating the worst survival for a combined recurrence type.[22] Additionally, the amount of peritoneal involvement significantly influences CSS. Yet this finding is not new, and it undermines once more a key principle of CRS: the imperative to achieve a complete resection.[6] The critical question for adequate selection remains the maximal tumor load for CRS/HIPEC. While in patients with DPAM curative resections are possible with maximal peritoneal dissemination, an increasing body of evidence demonstrates a significantly decreased survival rate for patients with CRC and a PCI of >15 or >17, respectively.[23,24]

A new and substantial finding of our analysis is the identification of major postoperative complications as a significant risk factor influencing CSS and DFS (Fig. 2). It is noteworthy that this impaired survival does not refer to mortality in the postoperative course but rather to long-term oncologic outcome. Large case series have shown that CRS/HIPEC can be performed with acceptable morbidity and mortality rates, which could be confirmed by analysis of our own patient cohort.[8,25] However, major complications being a risk factor for long-term survival has only come into focus recently, with conflicting results.[26] A recent study found postoperative complications requiring interventions to be predictive of early recurrence in CRC patients and consequently impaired OS.[27] In contrast, another study could not find any influence of a prolonged intensive care unit stay or readmission on long-term survival.[28]

There are several possible explanations for this observation. Patients necessitating extensive resections have an elevated risk of microscopic incomplete resections and therefore an increased risk of early tumor recurrence.[27] More extensive resections with prolonged operation time and colonic resections also place the patient at an increased risk for postoperative complications like fistulas or

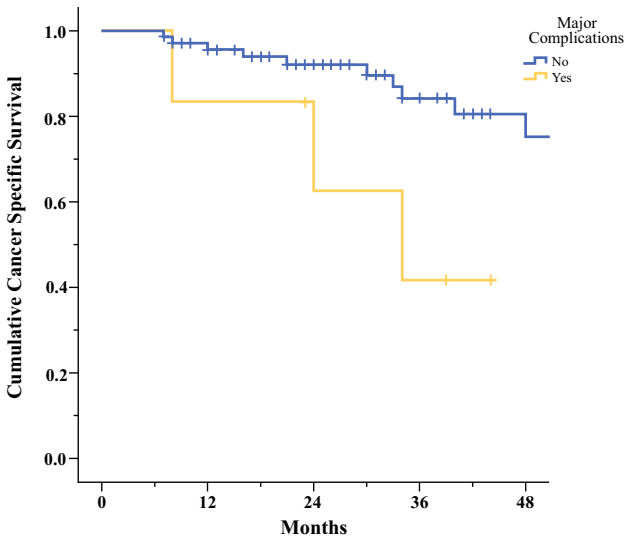

FIG. 2 CSS after complete CRS/HIPEC ($n = 76$) according to major complications. Patients with major complications in postoperative course ($n = 6$), defined as Clavien-Dindo IIIB or higher, had significantly worse long-term outcome with median CSS of 34 months only compared to patients without major complications ($n = 70$) ($p \leq 0.026$). *Vertical bars* imply censoring event. Analysis was performed via construction of Kaplan-Meier curves. Mantel-Cox log rank test was used to test for differences between groups

infections.[29] Infectious complications are among the most frequent after CRS/HIPEC.[25,29–31] Extensive surgical trauma as well as sepsis lead to a phase of immunosuppression termed compensatory anti-inflammatory response syndrome after an initial proinflammatory state known as systemic inflammatory response syndrome.[32,33] Occurrence of complications might therefore disturb the already delicate postoperative immunological balance in these patients, multiplying the postoperative immunosuppressive state. It has furthermore been demonstrated that HIPEC itself can induce immunosuppression as a result of hematologic toxicity and systemic absorbance of the chemotherapeutics used.[34] Factors of HIPEC, which influence the extent of immunosuppression, are the chemotherapeutic agents used as well as performance of splenectomy, which so far yields conflicting results regarding whether it mitigates or increases hematologic toxicity.[34–36]

When we consider these data together, we speculate that the already disturbed immunological balance is further shifted toward immunosuppression with the occurrence of infection-entailed major complications. This might block effective elimination of remaining systemic or peritoneal tumor cells by cytotoxic T cells and natural killer cells. This state of immunosuppression might also enable circulating tumor cells, which can be detected in up to 50% of patients before CRS/HIPEC, to escape elimination and more easily seed to new, different locations.[37] This would

directly affect DFS and CSS. Further research on this topic is highly warranted.

Our study has several restrictions. It is limited by its retrospective nature. The small sample size and low event-to-variable ratio prevent further subgroup analysis during Cox regression analysis and could potentially be prone to bias. Conclusions might therefore require confirmation in additional patient cohorts.

However, the factors identified in this study might prove helpful in the individual preoperative assessment and selection of patients. Major complications should be avoided whenever possible—not only in regard to perioperative morbidity and mortality, but also in the interest of the long-term oncologic outcome of patients with PC.

CONCLUSIONS

Outcomes after complete CRS/HIPEC are excellent for LG appendix tumors. A majority of well-selected patients with PC from CRC and HG appendix tumors will have a survival benefit.

Extent of peritoneal tumor spread, lymph node invasion, and major perioperative chemotherapy affect long-term CSS after CRS/HIPEC. Adequate selection of patients and avoidance of major complications whenever possible therefore remains critical for CRS/HIPEC.

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